## REMARKS

Claims 1-12, 20, 21, 35, 41, 58, and 59 were examined and rejected.

Claims 2, 29, 41, 42 (withdrawn) and 59 have been amended. Claim 58 is being canceled.

The amendment of claims 2 and 59 are discussed in more detail below. Withdrawn claim 29 is amended to remove spurious commas. Claims 41 and 42 are amended to correct their dependencies.

New claims 60 and 61 have been added to expressly include the feature of "improved targeting" of the modified catalase into peroxisomes (and are parallel to claims 1 and 20, respectively). This language is supported by the specification, at least at page 46, lines 13-16, and in Figure 9.

Claims 13-19, 22, 45-53, and 56-57 were previously withdrawn by Applicants pursuant to a Restriction Requirement. Of these, claims directed to the PST2 targeting sequence (claims 13-16, 22 and 25, 48 and 57) are being canceled. Claims 24, 26, 29, 34, 36, and 42 were withdrawn by the Examiner. Claims 27-28, 30-33, 37-40, 43-44, and 54-55 were previously canceled.

Thus the currently pending claims are claims 1-12, 17-21, 23, 24, 26, 29, 34-36, 41, 42, 45-47, 49-53, 56 and 59-61. **Of these, the active claims under examination are claims 1-12, 20, 21, 35, 41, and 59-61.**

None of the amended or new claims include new matter and their entry is respectfully requested.

Applicant thanks Examiner Prouty for her careful examination of the pending claims, her review of Applicant's proposed claims and for her courtesy during the interview conducted on November 6, 2008, and thereafter in crafting the Interview Summary.

### I. Objection Under 37 C.F.R. § 1.75(c)

The Examiner objected to claim 58 under 37 C.F.R. § 1.75(c), for failing to further limit the subject matter of claim 1. The cancellation of claim 58 renders this objection moot.

### II. Rejection Under 35 U.S.C. § 112, 2nd paragraph

Claims 2-11, 21, and 59 were rejected as being indefinite because claim 2 is allegedly "confusing" due to its reciting ***n*** additional amino acids to the amino-terminal side of $Xaa_{-3}$, which is necessarily present in catalase. Claim 2 has been amended to recite that the *replacement*

*sequence* comprises ***n*** additional amino acids to the amino-terminal side of $Xaa_3$. The Examiner indicated during the interview that this amendment (as proposed) would overcome the rejection.

The Office Action further stated that claim 59 is confusing due to its use of the phrase "primer being represented by SEQ ID NO: 18." Claim 59 has been amended to recite that "the four C-terminal amino acids are encoded by the coding nucleotides from a reverse primer, "the sequence of which is SEQ ID NO: 18." The Examiner also indicated that such an amendment, as proposed, would be adequate. Thus, the rejections under § 112 are believed to be moot.

## III. Rejections Under 35 U.S.C. § 103(a): Obviousness

### A. Rejection of Claims 1-6, 9-12, 35, 41, 58, and 59 Based on Sheikh and Trelease

The Examiner rejected claims 1-6, 9-12, 35, 41, 58 and 59 as obvious over

(1) F.G. Sheikh, *et al.*, "Abnormality in Catalase Import Into Peroxisomes Leads to Severe Neurological Disorder," *Proc. Natl. Acad. Sci. USA 95*:2961-66 (1988) (hereinafter "Sheikh"); and

(2) R.N. Trelease, *et al.*, "Rat Liver Catalase Is Sorted to Peroxisomes by Its C-Terminal Tripeptide Ala-Asn-Leu, Not by the Internal Ser-Lys-Leu Motif," *European J. Cell Biol.*, *71*:248-58 (1996) (hereinafter, "Trelease").

### B. Applicants' Response

#### 1. Legal Test for Obviousness

*In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988), set out the legal test for, and burden on the Office in, establishing a *prima facie* case of obviousness. The Federal Circuit has repeatedly articulated the requirements of a proper analysis:

> [W]here claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under Section 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *See In re Dow Chemical Co.*, ... 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure.

*Fine*, 5 USPQ2d at 1598.

### 2. Combination of References, Motivation/Suggestion and Hindsight Analysis

The Federal Circuit, in *Alza Corp. v. Mylan Laboratories, Inc.*, 80 USPQ2d, 1001 (Fed. Cir. 2006), devoted significant attention to this issue and cited extensively from its decision opinion in *In re Kahn*, 441 F.3d 977, 985, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006):

> As we explained in *Kahn*, The motivation-suggestion-teaching test picks up where the analogous art test leaves off and informs the *Graham* analysis. To reach a **non-hindsight** driven conclusion as to whether a person having ordinary skill in the art at the time of the invention would have viewed the subject matter as a whole to have been obvious in view of multiple references, the Board must provide some **rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct.** The requirement of such an explanation is consistent with governing obviousness law . . . .

441 F.3d at 987 (emphasis added).

The *Alza* court noted at 1004, that

> At its core, our anti-hindsight jurisprudence is a test that rests on the unremarkable premise that legal determinations of obviousness, as with such determinations generally, should be based on evidence rather than on mere speculation or conjecture. Our court's analysis in *Kahn* bears repeating:
>
> > A suggestion, teaching, or motivation to combine the relevant prior art teachings does not have to be found explicitly in the prior art, as "the teaching, motivation, or suggestion may be implicit from the prior art as a whole, rather than expressly stated in the references. . . . The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the **nature of the problem** to be solved as a whole would have suggested to those of ordinary skill in the art." However, rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be **some articulated reasoning with some rational underpinning** to support the legal conclusion of obviousness. This requirement is as much rooted in the Administrative Procedure Act [for our review of Board determinations], which ensures due process and non-arbitrary decision-making, as it is in § 103.
>
> *Kahn,* 441 F.3d at 987-88 (quoting *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000)) (citations omitted) (emphases added).

The standard for obviousness rejections was recently further articulated by the Supreme Court in *KSR International v. Teleflex, Inc.*, 127 S. Ct. 1727, 1740, 82 USPQ2d 1385 (2007). "[W]hen the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." The Supreme Court in *KSR* did not deviate from the earlier position and cited the *Kahn* decision favorably. The burden remains on the Office to consider the specific facts and the invention as a whole.

### 3. The Law as Applied to the Facts of the Present Case

The rejection is respectfully traversed because neither Sheikh nor Trelease, alone or in combination, disclose or suggest the claimed modified catalase.

It respectfully is submitted that a legally sufficient *prima facie* case of obviousness has not been adduced because the cited art does not suggest that the present compositions nor the present methods, lacks a proper foundation for a motivation to combine Sheikh with Trelease, and further, with Fujiwara.

Applying the test for obviousness and the other aspects of the law of obviousness as discussed above, the cited prior art does not suggest to those of ordinary skill that they should make the claimed compositions and, as a matter of logic, could not have revealed that the invention could have been practiced with a reasonable expectation of success. Absent a hindsight analysis of Applicants' disclosure, there would be no guidance in the art itself that would lead to the combining of these references and how to combine these references so as to achieve the result of the claims at issue.

Claim 1 recites a modified human catalase polypeptide having a carboxy-terminal peroxisome targeting signal (PTS) that has been modified from a native sequence of Lys-Ala-Asn-Leu (SEQ ID NO: 1) by replacement of SEQ ID NO:1 in human catalase with a PTS comprising the sequence $Xaa_{-3}$-$Xaa_{-2}$-$Xaa_{-1}$, wherein, independently,

$Xaa_{-3}$ is Ser, Ala or Cys;

$Xaa_{-2}$ is Lys, Arg or His; and

$Xaa_{-1}$ is Leu or Met.

**a. Discussion of Sheikh**

As the Examiner acknowledges, Sheikh tested a native human catalase sequence to which was *fused* (added) the tripeptide serine-lysine-leucine (SKL) at the C-terminus (*i.e.*, the C-terminal sequence was KANL-SKL) to import catalase into the catalase-deficient peroxisomes of mutant cell lines. Sheikh at 2961-2962. Sheikh does not disclose or suggest *replacing* KANL with the claimed tripeptide as the replacement sequence. Moreover, Sheikh concluded that catalase is imported via a pathway other than that of the PTS1 sequence, thus teaching away from the modified catalase of claim 1:

> PTS1 is the carboxy-terminal tripeptide SKL or its variant (4-8) . . .
>
> * * *
>
> These observations suggest that in humans targeting of catalase is mediated by a pathway that is **independent** of PTS1R [the PTS1 Receptor] or PTS2R [the PTS2 Receptor].

Sheikh at 2961, right col. (emphasis added).

The standard for obviousness rejections was recently articulated by the Supreme Court in *KSR International v. Teleflex, Inc.*, 127 S. Ct. 1727, 1740, 82 USPQ2d 1385 (2007). "[W]hen the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious."

Applying the Supreme Court's position in *KSR* on "teaching away" to the present case, because Sheikh states that the PTS1 receptor is not involved in the targeting of catalase into peroxisomes, Sheikh would lead away from modifying the C-terminal sequence to improve its peroxisome targeting:

> The targeting of PTS1-containing proteins is mediated by a cytoplasmic receptor (PTS1R). This receptor binds PTS1-signal-containing proteins in the cytosol and delivers them to peroxisomal membranes via its interaction with the cytoplasmic SH-3-domain-containing peroxisomal membrane protein Pex13p (35-37).
>
> * * *
>
> Studies described in this article clearly show that PTS1R or PTS2R is **not involved** in the targeting of catalase into peroxisomes.

Sheikh at 2965 (emphasis added).

Sheikh also emphasizes the importance of the KANL sequence in targeting catalase to peroxisomes, further discouraging its replacement:

> However, recently it has [been][*sic*]shown that like the SKL sequence, the carboxy-terminal sequence KANL of catalase is **important and sufficient** to target catalase into peroxisomes in humans and yeast (15).

*Id.* at 2961 (emphasis added). Given this teaching, one of ordinary skill would have had no reason *to attempt or even to consider* replacing the KANL sequence of human catalase with the claimed C-terminal tripeptide (or longer) replacement sequence.

Although not specifically articulated in the Office Action, the apparent basis for the obviousness rejection is that the claimed modification of catalase would have been "obvious to try" coupled with a reasonable expectation of success. See: *Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in KSR International Co. v. Teleflex, Inc.*, Fed. Reg.. 72, No. 175 (Oct. 10, 2007) at 57529 (Rationale E) ("**KSR Guidelines**").

However, a fair reading of Sheikh, would lead one to conclude that the claimed catalase would neither have been "obvious to try" nor would there have been a reasonable expectation that the claimed replacement would succeed. Rather, Sheikh concluded that the inability to import

catalase into peroxisomes was attributable to a defect in the *import machinery* of the mutant cells, not in the C-terminal targeting sequence:

> These studies and the cytosolic distribution of ChAT-KANL clearly demonstrate that the cytoplasmic localization of catalase is due to a defect in the import machinery of catalase into the peroxisomes.

Sheikh at 2963, left col. Given the foregoing, one of ordinary skill would not have reasonably expected that any modification to the C-terminal sequence of human catalase, *a fortiori,* the specific replacement modification recited in claim 1, would enable, let alone improve, peroxisomal targeting.

The only motivation Sheikh offered for modifying native catalase (which was, notably, by addition, ***not replacement***) was to deliver it to the particular mutant cell lines that were being studied to determine whether the restoration of catalase would correct certain enzymatic defects. However, this motivation would not have reasonably led to the claimed catalase -- which includes a *replacement sequence* for KANL -- because it was enough to fuse (add) SKL to the C-terminus of the native catalase sequence to provide the desired increase in peroxisomal uptake by these mutant cells.

A recent published decision by the Board also supports Applicants' position. In *Ex parte Whalen. II* (Bd. Pat. App. & Int., 2008 July 23) (Exhibit A), in reversing an obviousness rejection, the Board concluded:

> "[W]hen the prior art teaches away from the claimed solution . . . obviousness cannot be proven merely by showing that a known composition **could have been** modified by routine experimentation or solely on the expectation of success; it must be shown that those of ordinary skill in the art would have had **some apparent reason to modify that known composition in a way that would result in the claimed composition**."

(emphasis added). This accurately describes the relationship Sheikh bears to present claim 1. Sheikh convincingly undergirds Applicant's position that there would have been no reason to **try** a catalase modified in accordance with claim 1. In other words, it would not have been "obvious to try," Applicant's claimed invention nor would there have been a reasonable expectation at the time it was made and the priority application filed, that it would have succeeded.

**b. Discussion of Trelease**

Trelease is similarly deficient. As the Action indicates, Trelease (at 255) tested one modified **rat** catalase protein in which the C-terminal ANL sequence was replaced with SHL. One cannot ignore the context -- that Trelease's purpose was to determine whether an **internal** rat catalase SHL

sequence could serve as a peroxisomal targeting signal. *Id.* Trelease determined that rat catalase with *either* the native C-terminal sequence (KANL) or the modified sequence (KSHL) could localize to the peroxisome. *Id.* at 251 (Table II). Trelease did not attempt to determine whether either sequence provided superior peroxisome targeting. Moreover, Trelease expressly teaches away from the modified catalase of claim 1, by concluding that the native KANL sequence is both *necessary and sufficient* to target catalase to the peroxisome:

> The intent here was to test the hypothesis advocated by several investigators (see above) that the internal PTS1 motif located in the C-terminal region of catalase was necessary for targeting and import to peroxisomes. The results did not support this hypothesis. They alternatively indicated that the **C-terminal tripeptide ANL-COOH was necessary and sufficient** for peroxisome targeting.

Trelease at 249 (emphasis added).

> The punctate immunofluorescence image illustrated in Figure 5b shows that **ANL** appended to the C-terminus of CAT is **sufficient** for redirecting CAT from the cytosol to peroxisomes.

Trelease at 254 (emphasis added). As with Sheikh, one of ordinary skill would have been led away from modifying catalase in the way recited in claim 1 because Trelease expressly states that the native C-terminal sequence is sufficient for targeting the peroxisome.

The foregoing explanation is dispositive of the Examiner's rejection of claims 1-6, 9-12, 35, 41, 58, and 59 *as articulated in the Office Action.*

***New Assertions Made by the Examiner During the Interview***

During the interview, Applicant pointed out that --at most-- Trelease suggests that either the native KANL or SHL would result in some degree of peroxisomal targeting. However, because there is no suggestion that one targeting signal is better than the other in targeting rat catalase, one of ordinary skill in the art would have had no reason to alter the native C-terminal sequence in rat (or, *a fortiori,* in human) catalase. In response, the Examiner then asserted (at the interview, and for the first time) that the ordinary artisan would know that, in the context of different nucleic acid or protein functions, modifying a sequence to be more like the "canonical consensus sequence" would improve the function of the nucleic acid or protein. Examples noted by the Examiner were promoter sequences (nucleic acids), Shine-Dalgarno sequences (nucleic acids), signal sequences (proteins), *etc.* See: Interview Summary, mailed November 14, 2008.

Applicant emphasizes first that this assertion was never raised in the Office Action and does not form a part of the basis for the rejections made therein. In light of Sheikh and Trelease's disclosures, as discussed above, this ***new*** assertion (that replacement of a sequence with a "canonical consensus sequence" would be *per se* obvious) is the only basis for the suggestion that it would have been "obvious to try" the modified human catalase of claim 1. Moreover, to the extent the Office's position regarding obviousness now relies on this assertion, it clearly constitutes a **new** ground of rejection.[1]

Second, the Examiner's assertion is completely unsupported in the record. To the extent the Examiner is relying on "common knowledge" of skilled artisans, she has not met the requirements for taking "official notice" as set forth in MPEP § 2144.03. *See e.g.*, *In re Sang-Su Lee*, 277 F.3d 1338, 1343 (Fed. Cir. 2002) ("The factual inquiry whether to combine references…must be based on objective evidence of record").

> Official notice unsupported by documentary evidence should only be taken by the examiner where the facts asserted to be well-known, or to be common knowledge in the art are capable of instant and unquestionable demonstration as being well known.

MPEP at § 2144.03.

> [W]hen the PTO seeks to rely upon a chemical theory, in establishing a *prima facie* case of obviousness, it must provide evidentiary support for the existence and meaning of that theory.

*In re Grose*, 492 F.2d 1161, 1167-68, 201 USPQ 57, 63 (CCPA 1979).

Third, the Examiner's unsupported assertion is clearly overshadowed by the more specific teachings of the cited references both of which teach away from the modified human catalase polypeptide of claim 1, provide no motivation to modify and show that the claimed modification would not reasonably have been expected to succeed in improving the peroxisomal targeting of catalase.

The pending dependent claims recite additional patentable features that further distinguish Sheikh and Trelease (and the combination thereof). For example, claim 3 which depends from claim 2 (which depends from claim 1) recites that the replacement sequence comprises between about 5 and about 17 additional amino acids to the N-terminal side of the tripeptide recited in claim 1. Sheikh does not even disclose the notion of a replacement sequence for KANL, and Trelease is similarly deficient. Claims 4-6 further recite varying numbers of additional amino acids (to the N- -

[1] In this case, it would thus be improper to now issue a final rejection based on this *new ground* of rejection. *See* MPEP § 706.07(c) (final rejection is improper if based on a new ground that is "not necessitated by applicant's amendment of

terminal side of the tripeptide replacement sequence of claim 1); this also distinguishes the cited references.

In view of the foregoing, reconsideration and withdrawal of theis ground for rejection are respectfully requested.

### C. Rejection of Claims 20 and 21 Based on Sheikh, Trelease, and Fujiwara

Claims 20 and 21 were rejected as obvious over Sheikh and Trelease as applied to claims 1-6, 9-12, 35, 41, 58, and 59 (as articulated in the Office Action, *but not in the interview*) and further in view of a third reference:

(3) C. Fujiwara *et al.*, "Catalase-less Peroxisomes--Implication in the Milder forms of Peroxisome Biogenesis Disorder," *J. Biol. Chem.* , *275*:37271-77 (2000) (hereinafter "Fujiwara")

Claim 20 recites a pharmaceutical composition comprising the modified human catalase polypeptide of claim 1 and a pharmaceutically acceptable excipient or carrier. Claim 21 recites a similar pharmaceutical composition comprising the modified human catalase polypeptide of claim 2.

Fujiwara does not compensate for the deficiencies of Sheikh and Trelease noted above nor does it add the requisite disclosure to apply it to pharmaceutical composition claims. Nowhere does Fujiwara disclose or suggest replacing a KANL C-terminal sequence of native human catalase with SKL (or the other variants thereof) as recited in claim 1. Furthermore, Fujiwara does not disclose or suggest pharmaceutical compositions of any kind, let alone those based on the modified human catalase of claims 20 or 21. Moreover, according to Fujiwara, the claimed pharmaceutical compositions would not reasonably have been expected to succeed in treating peroxisomal disease states such as the peroxisomal biogenesis disorders ("PB disorders") that were studied. *See* Fujiwara at 37271. The reference discloses:

- study of peroxisomal import of catalase and other peroxisomal proteins in CHO cells with a temperature sensitive mutation in the Pex2p receptor. *Id* at 37271-37272.
- demonstration that in cells with the mutant Pex2P receptor, native catalase was targeted to the peroxisome at a "permissive" temperature but not at a "nonpermissive temperature". *Id.* at 37271 and 37275.

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the claims nor based on information submitted in an information disclosure statement during the period set forth in 37 CFR 1.97(c)).

- that "catalase-less peroxisomes are the cause of the milder phenotypes of these [PB disorder] patients." *Id.* at 37271.

Importantly, however, Fujiwara concludes that the catalase deficiency stems from a defect in the *import machinery* not the catalase sequence:

> Catalase-less peroxisomes as well as peroxisomal ghosts are the structures that form on the blockade of the normal course of peroxisome biogenesis **because of a deficiency in one of the essential *PEX* gene products**. Thus, these structures reflect the processes of peroxisome biogenesis, even if they themselves do not represent the biogenesis intermediates. They are ready to accept the PTS proteins if the **correct PEX gene products** are supplied.

*Id.* at 37276 (emphasis added).

While Fujiwara acknowledged the existence of a "variant PTS-1, KANL," *Id.* at 37273, nowhere does this document suggest that the catalase C-terminal sequence could or should be altered (let alone "replaced") to improve peroxisomal targeting. Fujiwara teaches away from the claimed pharmaceutical composition in its emphasis on defects in the import machinery (*i.e.*, the "PEX gene products") as the basis of peroxisomal catalase deficiencies. Fujiwara gives no indication that any PB disorders can be effectively treated by any composition or method that does not "remedy" such import machinery defects. Thus, Fujiwara further establishes that the claimed pharmaceutical compositions would not have been reasonably expected, prior to the making of the present invention, to alter or improve the peroxisomal targeting of catalase.

Accordingly, reconsideration and withdrawal of this second ground for rejection under § 103 is respectfully requested.

New Composition Claims Reciting Improved Targeting

As noted at the start of the REMARKS section, new claim 60 (directed to a modified catalase) and 61 (directed to a pharmaceutical composition comprising this modified catalase) expressly include the feature of improved targeting. This language is supported by the specification, *e.g.*, at page 46, lines 13-16, and in Figure 9. For the same reasons discussed above with respect to the other claims, these new claims are non-obvious over both combinations of the three cited references.

## IV. CONCLUSION

Applicant respectfully submits that the pending claims are in condition for allowance and earnestly urges such allowance.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By /Shmuel Livnat/
Shmuel Livnat
Registration No. 33,949

Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528

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